Long-term outcomes of initial experience of computer navigated pelvic and sacral primary bone tumour resections: soft-tissue margins must be adequate to reduce local recurrences.

Journal:	*The Bone & Joint Journal*
Manuscript ID	BJJ-2018-0981.R1
Manuscript Type:	Original Article
Keywords:	Pelvic sarcoma, Computer assisted navigation, Local recurrance, Soft-tissue margins

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We declare no conflict of interest

No funding was received.

Word count: 2775

Abstract

Background.

~~Pelvic tumours are difficult to treat, with large size at presentation, close proximity of viscera and neurovascular structures and a lack of neoadjuvant therapy.~~ Short-term outcomes using navigated surgery reduced surgical time, blood loss, intralesional resection rate and preserved function.

Aims

We investigated the local recurrence rate at extended follow-up in patients following navigated resection of primary pelvic and sacral tumours.

Methods

This prospective cohort study comprised 23 consecutive patients between 2010 and 2012 undergoing primary pelvic and sacral tumour resection using computer navigation. Local recurrence (LR) and mortality rates were calculated using the Kaplan-Meier method.

Results

Bone resection margins were all clear, with no bony recurrence. At a median follow-up of 6.0 years, eight patients (34.8%) developed soft-tissue LR with an overall cumulative LR rate at 6-years of 35.1% (95% CI=19.3-58.1%). Overall cumulative all-cause mortality rate at 6-years was 26.1% (95% CI = 12.7%-49.1%).

Conclusion

Despite the positive early experience with computer navigation-assisted resection LR rates remain high. With increasing knowledge of the size of soft tissue margins required to reduce LR and the close proximity of native structures in the pelvis, we advise against compromising resection to preserve function and encourage surgeons to reduce LR by prioritising wide tumour resection margins. Computer navigation remains a useful tool to aid pelvic tumour resection, but adequate soft tissue margins remain essential.

Introduction

The oncological outcomes of patients with primary tumours located in the pelvis or sacrum are worse than tumours originating at the extremities (31% vs. 51% 10-year overall patient survival)[1]. In the pelvis, tumour size is larger at presentation and the close proximity of visceral and neurovascular structures makes it difficult to achieve adequate surgical clearance[2],[3]. Half of patients experience surgical complications[2]. Furthermore, we lack neo-adjunctive chemoradiotherapy to downstage tumours or treat marginal resections in chondrosarcoma and chordoma, which are the predominant tumour histiotypes in the pelvis. Han et al, 2010 reported a mean 5-year recurrence-free survival rate of 45% for primary pelvic sarcomas[2], with local recurrence rates for sacral chordoma reported to be as high as 65% at 5-years[4]. Chondrosarcoma has a local recurrence rate of 38%, such recurrence being associated with higher histological grades[5]. Oncological outcomes of pelvic osteosarcoma, chondrosarcoma and sacral chordoma can therefore be improved[4,6,7].

Computer navigated surgery was introduced to improve the precision of bone resection and achieve clear margins whilst minimising the loss of disease-free tissue[8]. Salvage of disease-free tissue favours reconstruction, limb salvage and preserves patient function[9,10].

We have previously reported our initial experience with computer navigated resection of pelvic and sacral tumours. The technique was safe and effective in reducing intralesional resections (8.7%) compared to non-navigated resections (27%)[11]. We also noted reduced blood loss, surgical time and universally clear bone resection margins. A number of studies have since published comparable results using navigation for these tumours[12-17]. Despite this increasing body of evidence, it is unclear what the local recurrence rate with longer-term follow-up will be. Therefore, we lack evidence to support any benefit of navigation over traditional surgical techniques when managing these difficult tumours. This is important, as navigation does not guide soft tissue resection, where margins are most commonly compromised during surgery[18,19]. Compromised resection margins are a poor independent prognostic factor for most histological tumour types[20].

In 2012 the senior authors published data on 539 patients with primary pelvic bone tumours treated at the same institution without navigation. The 10 year mortality rate was 31% [1]. Rates of wide surgical margins were lower in pelvic compared to extremity tumours, with a local recurrence rate of 27%[1].

Aim

We investigated the outcomes at extended follow-up in 23 patients who had undergone computer navigated surgical resections for primary pelvic and sacral tumours. The primary outcome of interest was the rate of local disease recurrence. Secondary outcomes included the rates of further surgery and all-cause mortality.

Patients and Methods

This was a study of patients who underwent computer navigated limb salvage surgery for primary tumours of the pelvis or sacrum at a single specialist musculoskeletal oncology centre between April 2010 and 2012. Navigation was deemed appropriate in these patients because of the complex anatomy of the tumour and/or the perceived difficulty of achieving an adequate resection margin and accurate positioning of the implant using standard surgical methods. Patients who required hindquarter amputation or an uncomplicated distal sacrectomy underwent surgery without the use of navigation.

CT and MRI images were fused by an oncology-specific navigation system (Stryker Orthomap 3D Navigation System II; Stryker, Kalamazoo, Michigan). These fused images provided an accurate pre-operative three-dimensional (3D) model of the tumour, which was correlated with the patient's anatomy at the time of surgery. The surgeon was then able to use these images to plan the plane of the surgical resection margins in the workstation before undertaking the procedure. Navigated surgery enabled sacral nerve root preservation (n=10), limb salvage (n=4) and also permitted reconstruction rather than a hanging hip (n=2). Table 1 reports individual patient and tumour characteristics.

Table 1 Patient demographics and surgery performed with computer-assisted navigation (n=23)

Patient number	Age (years) / Sex	Diagnosis	Tumour location*	Maximum tumour size (cm)	Surgery performed
1	56M	Chondrosarcoma	P2	7	Excision + EPR**
2	34F	Osteosarcoma	P1+P4	3	Excision + fibular strut graft
3	40F	Chondrosarcoma	P2	16	Excision + EPR
4	69M	Chondrosarcoma	P1+P4	14	Excision alone
5	64M	Chondrosarcoma	P1+P2+P3	8.5	Excision + EPR
6	60M	Chondrosarcoma	P2+P3	8	Excision + EPR
7	73M	Chondrosarcoma	P2+P3	7.5	Excision + EPR
8	73F	Chordoma	Sacrum	8	Excision alone
9	22F	Osteosarcoma	P1+P4	11	Excision alone
10	45M	Osteosarcoma	P1+P2	6	Excision + 'ice-cream' cone
11	65F	Chordoma	Sacrum	7	Excision alone
12	73M	Chordoma	Sacrum	12.5	Excision alone
13	63M	Chordoma	Sacrum	11.5	Excision alone
14	26M	Ewing's sarcoma	P1+P2+P3	13	Excision alone
15	41M	Chondrosarcoma	P2+P3	7	Excision + EPR
16	48F	Chondrosarcoma	P2	5	Excision + EPR
17	21M	Chondrosarcoma	P1+P2+P3	20	Excision, irradiation and reimplantation of hemi pelvis + tricortical bone graft
18	70F	Chordoma	Sacrum	12.5	Excision alone
19	70F	Chondrosarcoma	P3	6.5	Excision alone
20	13M	Local recurrence of Irradiated Ewing's sarcoma	P1+P2	8	Excision alone
21	77M	Chordoma	Sacrum	10	Excision alone
22	58M	Chondrosarcoma	P1+P2+P3+P4	13	Excision + EPR
23	14F	Ewing's sarcoma	Sacrum	4	Excision alone

Abbreviations

M = male; F = female; EPR = endoprosthetic replacement

* Location of tumour and subsequent resection required classified according to Enneking *et al.* [21]: P1 = iliac bone; P2 = periacetabular region; P3 = superior and inferior pubic rami; P4 = hemisacrum.

** All endoprosthetic replacements used were custom-made implants

Information regarding patient selection, pre-operative planning, operative technique and post-operative regimen has previously been described[11]. The registration error was <1mm in all cases. All margins were planned on the navigation cases to be clear of tumour and provide an adequate margin to reduce the risk of local recurrence without compromising vial structures through the resection. The margins were planned to take into consideration the histological tumour type, the grade and location of the tumour. Resection margins were considered adequate if greater than 2mm for osteosarcoma and other subtypes, with 4mm specifically considered adequate for high grade chondrosarcoma[22,23]. Adjunctive therapy use varied by histological subtype. Patients with Ewing's sarcoma and osteosarcoma routinely had neo-adjunctive chemotherapy as per international guidelines[24,25]. A single patient with high-grade chondrosarcoma had adjunctive chemotherapy to chest metastasis.

All patients were reviewed in clinic at three monthly intervals for the first two years and at six monthly intervals thereafter as per national guidelines[26 27]. At each visit patients were examined to assess for any clinical signs of local recurrence with radiographs of the pelvis (antero-posterior view plus lateral of any implants) and chest performed. MRI scans were also performed at six monthly intervals to assess for local recurrence and interval changes. Local recurrence was defined as any detectable local disease at follow-up, occurring either alone or in conjunction with generalised recurrence, in patients who have undergone resection. Mortality data was verified using the summative care database, which records mortality data for England, Wales and Northern Ireland.

No patient was specifically recalled for this study with all data collected from clinical records and imaging systems as part of routine patient follow-up. Institutional review board approval was not required.

Statistical analysis

All analyses were performed using SPSS version 21.0 software (IBM Co., Armonk, NY). Local recurrence and mortality rates were calculated using the Kaplan-Meier method. Time to event, from date of surgery, was established and patients censored according to status (alive or dead) or local recurrence.

Covariates (patient and surgical) were compared between patients with and without local recurrence depending on data distribution. Numerical variables with a normal distribution (patient age) were compared using unpaired t-tests. To compare medians in non-parametric distributions, we used Mann Witney U-tests. Categorical data were compared using Fishers' exact tests. Due to the small size of the cohort and the limited number of outcomes recorded, it was not possible to meaningfully investigate the effects of each or multiple covariate(s) on local recurrence rates with logistic regression models. The significance level for all analyses was $p<0.05$, with 95% confidence intervals (CIs) also used.

Results

The study comprised 23 patients with primary pelvic or sacral tumours who underwent navigated resection. Nine of the patients were female and mean age at presentation was 51 years (10 to 77years, SD 21.1). Median follow-up of patients was 6 years (IQR 5.16 to 6.3years) with minimum follow-up of 4 years.

The median tumour size at presentation was 8cm (IQR 7 to 12.5). Histological tumour subtypes were: intermediate or low-grade chondrosarcoma n=8; sacral chordoma n=6; high-grade chondrosarcoma n=3, Ewing's sarcoma n=3; high-grade osteosarcoma n=2 and low-grade osteosarcoma n=1.

Clear bone resection margins were achieved in all cases. Margins were compromised in two cases, thus 8.7% of the primary tumours had an intralesional resection. Both of the patients suffered a local recurrence (Table 2).

Local recurrence

During the study period eight patients developed local disease recurrence, Table 2. The overall cumulative local recurrence rate at 6-years was 35.1% (95% CI=19.3-58.1%), refer to Figure 1.

Original patient number	Histological subtype	Soft-tissue margin (mm)	Bone margin (mm)	Max tumour diameter (mm)	Time to LR (m)	Metastasis (m)	Further Surgery (m)	Final status
1	Chondrosarcoma	2	5	7	29	No	Hindquarter amputation (31)	NED
5	Chondrosarcoma	Intralesional	5	8.5	12	Lung (16)	Excision of local recurrence (13)	DOD
7	Chondrosarcoma	6	5	7.5	14	Lung (15)	Hindquarter amputation (16)	DOD
8	Sacral Chordoma	1	10	8	18	No		AWD
11	Sacral Chordoma	1	9	7	15	T6 (54)	1) Excision of local recurrence (20); 2) En block resection T6 met (55); 3) Revion En block resection and fusion L3 to S1.	AWD
13	Sacral Chordoma	Intralesional	20	11.5	15	Lumbar spine (36)	Excision of local recurrence (48)	AWD
19	Chondrosarcoma	1	30	6.5	7	L4	Hindquarter amp (?) Excision of local recurrence (8 and 45)	AWD
22	Chondrosarcoma	5	10	13	7	Lung (10)		DOD

Table 2. Histopathological resection results and clinical outcomes in patients with local recurrence (n=8). **Abbreviation:** DVT = deep vein thrombosis; NED = no evidence of disease; AWD = alive with disease; DOD = died of disease

Tumour recurrence stratified by histological subtype was as follows: chondrosarcoma 45% (n=5) and sacral chordoma 50% (n=3). No recurrence was seen in Osteosarcoma or Ewing's sarcoma patients. Patients who suffered a local recurrence were older was higher (mean age 43 vs 65 years, p=0.006; Table

3). There were no other tumour or surgical covariates which were significantly different between patients with and without local recurrence.

Variable	Without LR	With LR	Significance
Number of patients	n= 15	n= 8	
Mean Age (years)	43 (SD 23, 95% CI 31 to 56	65 (SD 6.6, 95% CI 60 to 71)	0.006
TUMOUR GRADE: Low Grade	n= 8	n= 3	
Intermediate Grade	n=2	n= 3	
High Grade	n= 5	n= 2	0.296
Median tumour size (cm)	10 (7*)	7.8 (8*)	0.591
Median bone resection margin (mm)	10 (5*)	9.5 (13*)	0.957
Median soft tissue resection margin (mm)	3 (3*)	1 (6*)	0.190
Proportion inadequate soft tissue margin	33%	60%	0.144

Table 3. Patient and tumour variables in patients with and without local recurrence. LR = Local recurrence, * = Interquartile range

Three of the eight patients who suffered a local recurrence have died (mean time to death=18months (SD 7.2). Three hindquarter amputations were performed as a secondary procedure for local recurrence. Four patients had limb salvage excision for recurrent lesions. Non-operative treatment for local recurrence was chosen by two patients. Of eight patients with local recurrence one patient has no evidence of disease, the remaining 4 patients are alive with disease.

Of the 23 patients included in the study, six patients (26.1%) died at a mean time of 2.3 years (1.0 to 3.8 years) from surgery. The cumulative 5-year all-cause mortality rate was 26.1% (95% CI = 12.7%-49.1%), refer to Figure 2. In total 12 patients avoided death or local recurrence at last follow-up.

Further Surgery and complications

Table 2 reports secondary surgery for oncological indications, metastasis and the current status of the patient. Further surgery performed, in addition to that for local recurrence, included hip manipulation under anaesthetic following dislocation (n=4); wound debridement following infection (n=3) and local metastasis excision (n=2). Two patients suffered a sciatic nerve palsy following their original surgery. A 21-year-old patient with radiation induced high grade osteosarcoma of the right iliac wing measuring 11cm underwent a hindquarter amputation 14 months after the original excision, following the diagnosis of a skip lesion. The patient died of metastatic disease 2.5 years later.

Discussion

Our initial outcomes following computer navigation assisted surgery were encouraging with an intralesional resection rate of 8.7% and local recurrence rates of 13% up to one-year after surgery[11]. This study adds to the evolving literature by demonstrating the importance of the soft tissue margin, and not just the bone margin, when assessing the risk of local recurrence. The role of the margin in local recurrence is an evolving subject and whilst much remains unknown, there is evidence that the risk of local recurrence following resection is a composite function of histological variant, grade, location and quality of the tissue comprising the margin. In an unpublished series of 1077 patients with local recurrence, we found that 89% occurred within five years of diagnosis and the median time to local recurrence was fifteen months. Thus, we are confident that the follow-up (median 6-years) reported has sufficient follow up to debate oncological outcomes.

Computer navigated surgery improves the precision of bony resections, enabling the surgeon to conserve native tissue in favour of limb reconstruction and preserve adjacent neurovascular structures[9,28-30]. In this series we achieved wide bone clearance in all patients with no failure in navigation, but we are disappointed with the soft-tissue recurrence rate. The degree of soft tissue resection was assessed on a individual case basis and all macroscopically compromised soft tissue was removed with the tumour. Rather than planning a wider bone margin, our findings make it clear that greater attention must be paid to the soft tissue dissection. In fact, it may be that a wider soft tissue margin should be considered to allow a narrower bone resection margin. Soft-tissue margins are independent prognostic factors for local recurrence and survival, with restricted access in the pelvis and no interfacial planes to resect these large tumours, thus obtaining clear soft-tissue margins remain a challenge[2]. Even when using navigation, studies report soft-tissue recurrence rates of 20 to 25% at short-term follow-up[8,12,14,20].

Since publication of the original series in 2013, the authors have defined minimal soft tissue margins when resecting high grade osteosarcoma and high grade chondrosarcoma tumours to be 2mm and 4mm respectively[22,23]. Wide resection margins improve local recurrence rates in sacral chordoma patients[4]. Yang et al, 2016 obtained a minimal 15mm soft tissue margin when resecting primary sacral chordomas (n=26), and reduced local recurrence rates to 7.7% at 38 months[15]. The use of chemoradiotherapy in planned intralesional resections also demonstrated benefit[19].

We have demonstrated that navigation can achieve clear margins at the bony margin but this should not be at the compromise of the soft tissue margin. Equally, whilst we have demonstrated the efficacy of navigation in retaining critical structures, particularly nerve roots for sacral resections, we are yet to define the acceptable margins in many of these histological subtypes. Whilst navigation allows a resection close to the tumour, preserving critical structures, the basic principle of resection aimed at minimising the risk of local recurrence must not be overlooked, even if this necessitates sacrifice of vital neurological, vascular or visceral structures[20]. When considering the devastating natural history of these tumours, we feel navigation surgery offers limb salvage and can preserve bladder/ bowel function and mobility. Preservation of life must be considered the primary aim of any treatment for a pelvic sarcoma, although respect to quality of life and functional restoration is important to discuss with the patient when considering surgical options. However, as surgical margins are a very important predictor of outcome, the first goal should always be to achieve adequate margins[13].

The authors have published several papers showing that computer navigated surgery in the pelvis has several benefits including reduced blood loss, reduced complication rates, reduced intralesional rates at surgery and higher disease free survival[31,32]. This study must be taken in context, as it reports the first 23 patients out of over 100 patients that have undergone navigated surgery. Clearly, though a technical learning curve was mastered quickly, a more philosophical learning curve combined with further evidence about the width of an adequate margin was appreciated with time. The authors remain supportive that computer navigation reduces positive margins at surgery, and it remains routinely used for pelvic sarcoma cases. However, we now strive to achieve more radical soft tissue margins when possible.

In 2012 the senior authors published data on 539 patients with primary pelvic bone or sacral sarcomas treated at the same institution. The cohort had a ten-year overall mortality of 31%[1]. At five years the current study had a cumulative mortality rate of 27.1%. Cho et al, 2012 reports a three-year survival rate of patients with pelvic tumours of 80.0% (95% CI 55.3 to 100)[12]. Overall survival for sacral chordoma treated without navigation is 97%, 71% and 47% at 5, 10 and 15 years respectively[4]. Chondrosarcoma and osteosarcoma have poorer survival at five years, 72% and 27% respectively[33,6]. In keeping with evidence our study suggests that chordoma tends to recur locally with no patients dying during the period observed. In contrast, high grade chondrosarcomas, osteosarcomas and Ewing's sarcoma, with aggressive biology, can lead to patient deaths.

This study had limitations. Our hospital is a tertiary sarcoma unit treating bone sarcomas for an overall population of 22 million people. We have a stringent follow-up protocol and offer satellite clinics, but some complications may have been treated locally and unknown to us. However, we are confident in the local recurrence and mortality data. To determine the origin of local recurrences we relied upon cross sectional imaging, histology reports and senior surgeon clinic consultations. We feel this is sensitive enough to dichotomize into soft tissue or bone as the site of recurrence and differentiate between skip lesions or adjacent metastasis. Subgroup analysis, including the ability to perform regression modelling, was limited by the sample size and the relatively small number of events. A limitation of this study is that the histopathology specimens were not reassessed retrospectively for this study. Due to the nature of this study and the extended follow-up from the initial report we did not feel it was necessary for these specimens to be re-reviewed in this manner. However, these specimens were prospectively assessed by experienced histopathologists at our specialist/tertiary oncology centre, and subsequently considered in detail in our weekly multi-disciplinary team meetings (which also include the surgeons and radiologists). Therefore, we consider the data presented regarding the histopathological specimen analysis is robust for the purposes of this particular study. It was not the remit of this study to compare to a matched cohort. However, future work could encompass a retrospective case control study of comparable tumours between navigation and non-navigation assisted surgery, assessing the risk of local recurrence and the functional outcomes of patients. However, given the rare and heterogenous nature of the tumours included, it may be difficult to build comparable groups which take into consideration the myriad of variables that are known to effect local recurrence and patient survival. For the purpose of this study we wanted to compare longer term outcomes of the patients included in the initial study and felt that comparing this to our own institutions historical data relays the same important message.

Conclusions

Following the positive early experience with computer assisted navigation resection of complex pelvic and sacral tumours reducing intralesional resection rates, we have now observed that similar local recurrence free survival rates were seen in navigated resections compared with our historical non-navigated resections. Although further research is needed to explain these observations, it is suspected that increasing age, advanced disease and tumour biology are important contributory factors. Computer navigation-assisted surgery provides clear bone resection margins and precise resection, but local recurrence rates are determined by the adequacy of soft tissue margins. We advise against routinely compromising the latter to preserve function, and we encourage surgeons to preserve life by prioritising clear soft-tissue resection margins.

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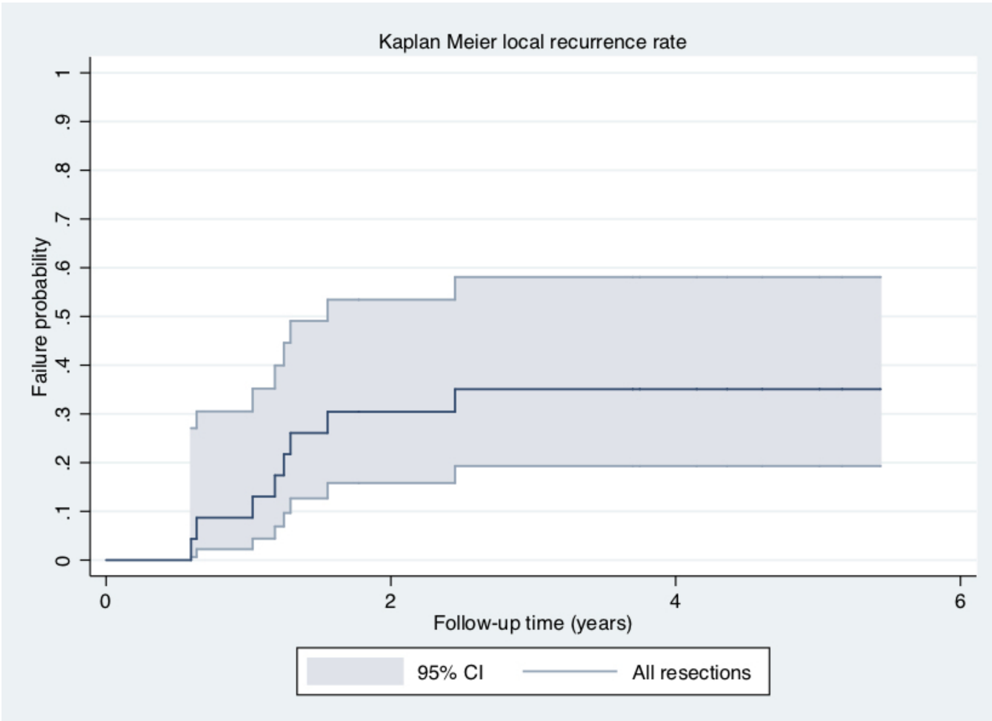
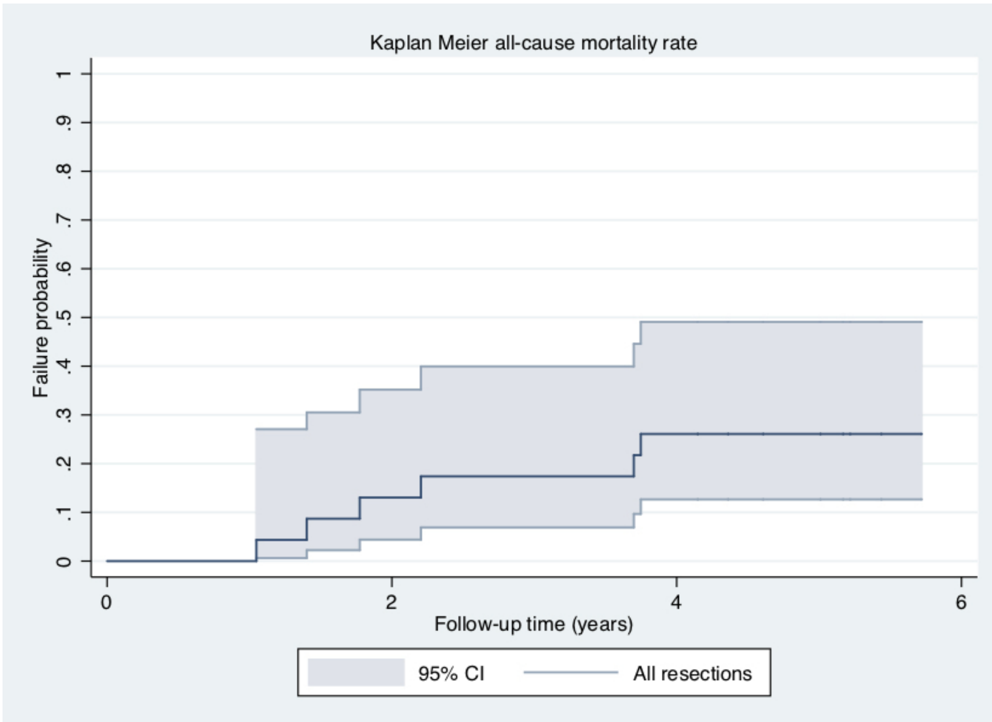


Kaplan Meier curve of local recurrence rates

139x101mm (150 x 150 DPI)



Kaplan Meier curve for all-cause mortality

139x101mm (150 x 150 DPI)